REMARKS

Applicant gratefully acknowledges the Examiner's helpful comments which he provided during a personal interview with Applicant on October 12, 2005. Applicant notes that the personal interview was attended by the Examiner, Applicant's undersigned counsel and a co-inventor Isadore Rigoutsos. At the interview, the parties discussed the rejections included in the Office Action dated July 25, 2005, and the claims, specifically, independent claims 1, 16, 23, 29 and 30.

In particular, at the interview, Applicant pointed out that the Examiner had failed to adequately support his restriction of claim 30, that claims 16-20, 22 and 23 were clearly patentable subject matter under 35 USC §101, and that the claimed invention was clearly not taught or suggested by the cited references.

Applicant notes that based on the arguments of the inventor at the interview, the Examiner conceded that the cited references (e.g., Nishikawa) does not appear to teach or suggest the claimed invention.

Claims 1-30 are all the claims presently pending in the application. Claims 1, 16, 23, 29 and 30 have been amended to more particularly define the invention. Claim 30 has been withdrawn by the Examiner as allegedly directed to an independent and distinct invention.

It is noted that the claim amendments are made only for more particularly pointing out the invention, and not for distinguishing the invention over the prior art, narrowing the claims or for any statutory requirements of patentability. Further, Applicant specifically states that no amendment to any claim herein should be construed as a disclaimer of any interest in or right to an equivalent of any element or feature of the amended claim.

Claims 16-20, 22 and 23 stand rejected under 35 U.S.C. §101 allegedly because the claimed invention is directed to non-statutory algorithm type subject matter.

Claims 1-6, 9-11, 13-21, 23 and 27-29 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Nishikawa ("An Integrated Analysis and Database System for Full-Length cDNA", *Genome Informatics*, 11:12-23 (2000)). Claims 1-29 stand rejected under 35

U.S.C. §103(a) as allegedly unpatentable over Nishikawa taken with Rigoutsos, et al. (COMBINATORIAL PATTERN DISCOVERY IN BIOLOICAL SEQUENCES: THE TEIRESIAS ALGORITHM, BIOINFORMATICS, Vol. 14, No. 1, Pages 55-67, 1998) (hereinafter, "the Teiresias paper").

These rejections are respectfully traversed in the following discussion.

I. THE CLAIMED INVENTION

The claimed invention (e.g., as recited in claim 1) is directed to a system for identifying genes. The system includes a pattern database comprising patterns of amino acids, and an input device for inputting a **genomic** DNA sequence.

Importantly, the system further includes a processor which translates an open reading frame (ORF) of the DNA sequence into an amino acid translation, and locates in the amino acid translation occurrences of the patterns from the pattern database to determine whether the open reading frame includes a putative gene in the DNA sequence.

Conventional systems for identifying genes (e.g., putative genes) are either based on the use the statistics of DNA sequences, or the use of similarity searches to determine gene locations (Application at page 2, lines 7-22). However, these conventional methods have various problems which prevent them from efficiently identifying genes in a given DNA sequence (Application at page 3, line 19-page 4, line 21).

The claimed invention, on the other hand, includes a processor which translates an open reading frame (ORF) of the DNA sequence **(e.g., a genomic DNA sequence)** into an amino acid translation, and locates in the amino acid translation occurrences of the patterns from the pattern database to determine whether the open reading frame includes a putative gene in the DNA sequence (e.g., a genomic DNA sequence) (Application at Figure 1; page 5, lines 4-11). The claimed invention may be considered as including the best characteristics of statistical approaches and database similarity searches, in identifying genes in a given DNA sequence (Application at page 6, lines 18-21).

II. THE RESTRICTION REQUIREMENT

The Examiner has withdrawn claim 30 from prosecution alleging only that claim 30 is "independent or distinct" from the invention originally claimed. However, Applicant would point out that the Examiner has clearly failed to support his restriction of claim 30 from prosecution.

First, Applicant respectfully submits that the Examiner cannot just make the vague assertion that claim 30 is "independent or distinct". Instead, the Examiner must state specifically in the Office Action whether he is alleging that claim 30 is independent of the originally claimed invention, or that claim 30 is distinct from the originally claimed invention, in order to allow Applicant to properly respond to the restriction requirement.

The Examiner must then support his allegation with facts. Here, however, the Examiner merely states that "claim 30 recites limitations which cause said claim to be distinct from the examined invention", which is clearly insufficient under MPEP §802.01.

Indeed, MPEP §802.01 defines the term "independent" (i.e., not dependent) meaning that there is no disclosed relationship between the two or more subjects disclosed, that is, they are unconnected in design, operation, or effect, for example: (1) species under a genus which species are not usable together as disclosed; or (2) process and apparatus incapable of being used in practicing the process.

Further, MPEP §802.01 also defines the term "distinct" as meaning that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice, process and product made, etc., but are capable of separate manufacture, use, or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER.

Nowhere has the Examiner alleged that the invention of claim 30 and the originally claimed invention are unconnected in design, operation, or effect (e.g., a species under a genus which species are not usable together as disclosed; or a process and apparatus incapable of being used in practicing the process), and thus, he has not alleged that claim 30 is **independent of** the

originally claimed invention. Further, nowhere has the Examiner alleged that the invention of claim 30 and the originally claimed invention are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice, process and product made, etc., but are capable of separate manufacture, use, or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER, and thus, he has not alleged that claim 30 is **distinct from** the originally claimed invention.

Moreover, even assuming (arguendo) that claim 30 is either independent or distinct from the original claimed invention, the Examiner has clearly failed to show that there would be some undue burden if the Examiner examined claim 30 with the other pending claims. Indeed, MPEP 802.01 states that "*a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search*". However, nowhere has the Examiner made such an allegation.

Therefore, Applicant submits that the Examiner has clearly failed to support his restriction of claim 30 from prosecution. Therefore, the Examiner is respectfully requested to withdraw this restriction requirement.

III. THE 35 USC §101 REJECTION

Claims 16-20, 22 and 23 stand rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory algorithm type subject matter. While Applicant respectfully disagrees with the Examiner, Applicant notes that in the interest of expediting prosecution, claims 16 and 23 have been amended to recite "*displaying a result of said determining whether said ORF includes a putative gene*", which the Examiner indicated in the personal interview would be sufficient to overcome this rejection.

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw this rejection.

IV. THE ALLEGED PRIOR ART REFERENCES

A. Nishikawa

The Examiner alleges that Nishikawa teaches the claimed invention of claims 1-6, 9-11, 13-21, 23 and 27-29. Applicant submits, however, that there are elements of the claimed invention which are neither taught nor suggested by Nishikawa.

However, contrary to the Examiner's allegations, Nishikawa does not teach or suggest an input device for inputting a **genomic** DNA sequence, and *"a processor which: translates an open reading frame (ORF) of said DNA sequence into an amino acid translation; and locates in said amino acid translation occurrences of said patterns from said pattern database to determine whether said open reading frame includes a putative gene in said DNA sequence"*, as recited, for example, in claim 1, and similarly recited in claims 16, 23 and 29.

As noted above, unlike conventional systems for identifying genes (e.g., putative genes) which are either based on the use of the statistics of DNA sequences, or the use of similarity searches to determine gene locations, the claimed invention includes a processor which translates an open reading frame (ORF) of the DNA sequence (e.g., **genomic DNA sequence**) into an amino acid translation, and locates in the amino acid translation occurrences of the patterns from the pattern database to determine whether the open reading frame includes a putative gene in the DNA sequence (Application at Figure 1; page 5, lines 4-11). The claimed invention may be considered as including the best characteristics of statistical approaches and database similarity searches, in identifying genes in a given DNA sequence (Application at page 6, lines 18-21).

Clearly, these features are not taught or suggested by the Nishikawa. Indeed, Applicant notes that the Examiner indicated at the personal interview that Nishikawa does not likely teach or suggest these features of the claimed invention.

Indeed, as the inventor Isadore Rigoutsos explained to the Examiner at the personal interview, Nishikawa is merely directed to an annotation and database system for full-length cDNA sequences (e.g., DNA sequences which were produced from mRNA by reverse transcription). That is, the use of cDNA sequences in Nishikawa **presumes that genes have**

already been identified in a DNA sequence. This is very different from the claimed invention which may be used to identify a putative gene in a genomic DNA sequence (e.g., a full complement of DNA contained in the genome of a cell or organism). Thus, it is completely unreasonable to attempt to equate the Nishikawa method with the **method of identifying genes** (e.g., locating in an amino acid translation of an ORF of a DNA sequence, occurrences of patterns from pattern database to determine whether the open reading frame includes a putative gene), as in the claimed invention.

In fact, Nishikawa describes his method as "a new method of functional annotation for full-length cDNA sequences based on a database of similarity search results" (Nishikawa at page 15, section 2.3.1(a)) (emphasis added). Specifically, the Nishikawa annotation system includes:

a) orf annotation

- conventional tools
- motif based system of retrieval and display

b) functional annotation

- using database results they characterize a given cDNA

c) mapping annotation

- they link full-length cDNA with DNA sequences already in the database

d) integrated retrieval and display

Nishikawa uses the data generated by the NEDO project. Here is the stated description and goal of the NEDO project: (from http://www.nedo.go.jp/bio-e/index_syokai.html)

"Full-length cDNA sequencing project and draft sequence of human genome

Institute of Medical Science, University of Tokyo

Sumio Sugano

With the completion of sequencing the chromosome 21 and 22 and 'draft' of human genome, the genome sequencing project of human entered its final stage. We may see "finished"

sequence of entire genome within few years. That will mark a transition from the era of structure genomics to that of functional genomics. The full-length cDNA is a crucial tool both for the annotation of the human genome and for the experimental analysis of gene function. Thus, we are conducting a large-scale collection and sequencing of full-length cDNA with the support of NEDO.

Last year, about 160,000 clones were isolated from more than 20 full-length enriched human cDNA libraries made by "Oligo-capping" method. Their 5's end sequences were determined. We selected about 10,000 putatively full-length cDNA using these sequence data and determined the entire sequence of the selected clones. This NEDO project will continue for another two years and aim to determine the sequence of 20,000 full-length cDNA clones in addition."

All of the sequences that Nishikawa processes are the output of the NEDO project: these are cDNA sequences that have been determined "biologically" and "not computationally." The problem with biological validation is that unless the experiment was carried out with the right tissue(s) and at the right time-point no mRNA will be derived and thus no cDNA either. This is precisely where the power of the claimed invention may be utilized.

It is important to stress that Nishikawa NEITHER DESCRIBES NOR CARRIES OUT ORF detection. Instead, the ORFs with which Nishikawa works are the result of the NEDO project and the output of biological (wet-lab) processes. Additionally, Nishikawa attempt to characterize the ORFs that they got from NEDO, in terms of

1. how long they are / whether NEDO's output corresponds to the full length cDNA;
2. what it is that the alleged corresponding protein product does functionally;
3. where it is that the alleged corresponding protein product will end up(intracellular, membrane, extracellular, or finer granularity); and
4. where the transmembrane regions are in the alleged corresponding protein product if the latter is *predicted* by steps b) and c) to be a transmembrane sequence.

In terms of characterizing what the alleged corresponding protein product does functionally, Nishikawa also carry out database searches and propose a method (that they erroneously claim is novel) for determining the functional behavior of the alleged product in combination with (2) above.

However, the claimed invention may do the exact opposite of Nishikawa. That is:

1) the claimed invention does NOT necessarily make any attempt to characterize the alleged corresponding protein product in any way; and

2) the claimed invention may CARRY OUT ORF detection using a computational process.

Further, it is important to note that unlike Nishikawa, the claimed invention does not necessarily involve a method for the **functional annotation** of full-length cDNA sequences. In fact, the claimed invention may have nothing to do with "functional annotation."

The Examiner further alleges that "Nishikawa uses the ORF annotation system for motif analysis, which represent patterns, and prediction [of] ORFs, cellular localization, and transmembrane regions which represent the identification of putative genes." This is simply an incorrect statement.

In fact, Nishikawa explicitly state at the beginning of their paper that they get their ORFs directly from the NEDO project; as such they **do NOT carry out ORF "prediction"** which is an important feature of the claimed invention. As a matter of fact, Nishikawa simply ameliorates the available ORFs by attaching other, presumably related information that could be of use to practitioners.

Thus, summarily,

a) Contrary to the Examiner's allegations, Nishikawa does NOT use the ORF annotation system to do motif analysis, (in fact, the very statement of the examiner is meaningless as a process)

b) Contrary to the Examiner's allegations, Nishikawa does NOT use the ORF annotation system to predict ORFs, (see comment above about the NEDO project)

c) The Examiner's allegation that "the prediction of ORFs, cellular localization, and transmembrane regions [which] represents the identification of putative genes" is an incorrect statement for at least the following 4 reasons:

1) no ORFs are predicted by Nishikawa ;

2) there is no such thing as an ORF's cellular localization, and transmembrane regions – the statement is meaningful only for proteins which are the products of the ribosome translating ORF transcripts;

3) even assuming (arguendo) that the Examiner's loose language (e.g., "ORF's cellular localization ...") is correct, knowing a protein's cellular localization, and transmembrane region is not tantamount to "ORF prediction"; and,

4) there is nothing putative about the genes used in the Nishikawa work: since these sequences are the result of the NEDO project it means that these sequences were the result of reverse transcription from messenger-RNA products that have been identified using wet-lab approaches, ergo the gene has been transcribed, ergo **Nishikawa is working with *bona fide* gene sequences.**

The Examiner further alleges thatthe use of Swiss-Prot as practiced by Nishikawa is for the purpose of discovering ORFs, which is clearly incorrect). Indeed, the claimed invention (e.g., claims 5 and 17) may include databases of patterns (e.g., of regular expressions that may be DERIVED from databases such as Swiss-Prot by means of a distilling method). Clearly, this manner of using Swiss-Prot is UNlike the use of Swiss-Prot by Nishikawa.

The Examiner alleges that Nishikawa uses the Prosite/PFAM databases precisely as in the claimed invention. However, Nishikawa does NOT engage in the act of DERIVING patterns from any of sequence databases that he mentions. Instead, **Nishikawa USES widely available pattern databases to characterize ALREADY KNOWN ORFs.**

The Examiner further alleges that the Nishikawa system "performs initiation codon analysis for IDENTIFYING ORFs by using ATGpr" as stated in Claim 9. This is an incorrect statement. In fact, Nishikawa makes use of the initiation codon analysis NOT TO IDENTIFY

ORFs but in order to determine whether the cDNA that they were handed by the NEDO project is a COMPLETE sequence (initiation codon is present) or a FRAGMENT of a complete sequence (initiation codon is absent).

The Examiner further alleges (Office Action at page 11) that "[s]imilarity level is defined as a function of alignment variables, such as identity, E-value, and consensus length of alignment ... which represents 'a predetermined number of pattern matches". However, the variables that Nishikawa uses and which the Examiner recites here, "E-value, consensus length of the alignment," are variables with values which are NOT correlated with the "number of pattern matches" that two sequences may be sharing. That is,

1. one can have two sequence segments that are quasi-identical → E-value is essentially equal to 0, yet the two sequence segments share few (or even no) patterns. Perfect example: the sequence in the database is a so-called 'pioneer' sequence, ergo single copy, ergo no patterns derived from processing the database, ergo no patterns in common between the "query" segment and the "database segment" even though the E-value suggest that they are quasi-identical; and

2. exactly the same argument can be made in the case of two sequence segments whose consensus length of the alignment is very high.

That is, contrary to the Examiner's allegations, there is no correlation between E-values/alignment length and patterns that are shared by the 'query' and the 'database' sequences.

The Examiner further alleges on page 11 of the Office Action, that BLASTX discloses a pattern matching algorithm. However, BLASTX and all its variants are NOT "pattern matching algorithms" but are "similarity searching algorithms." In any event, both of these are different from a "pattern discovery algorithm" which may be used in the claimed invention.

The difference between a pattern matching algorithm and a similarity searching algorithm is in fact a very fundamental one. The following definitions make this fundamental difference clear.

1. A similarity searching algorithm may be defined as follows: given a database D

of objects, a query object Q, a metric function d(.,.) that can compare any two objects, and a threshold T, a searching algorithm is to search D and report all objects C in D for which the following holds true: $d(Q,C) \leq T$.

2. A pattern matching algorithm may be defined as follows: given a database D of objects, and a pattern P, a pattern matching algorithm is to search D and report all objects C that contain one or more instances of P.

3. A pattern discovery algorithm may be defined as follows: given a database D of objects, and a threshold T, a pattern discovery algorithm is to process D and discover all patterns P (whose definition is unknown) that appear a minimum of T times in D.

Therefore, contrary to the Examiner's allegations, Nishikawa does **not** teach or suggest an input device for inputting a **genomic** DNA sequence, and certainly does not teach or suggest a processor which translates an open reading frame (ORF) of the DNA sequence into an amino acid translation, and locates in the amino acid translation occurrences of the patterns from the pattern database to determine whether the open reading frame includes a putative gene in the DNA sequence, as in the claimed invention.

Therefore, Applicant submits that there are elements of the claimed invention that are not taught or suggest by Nishikawa. Therefore, the Examiner is respectfully requested to withdraw this rejection.

B. The Teiresias Paper (Rigoutsos et al.)

The Examiner alleges that Nishikawa would have been combined with the Teiresias paper to form the claimed invention of claims 1-29. Applicant submits, however, that these alleged references would not have been combined and even if combined, the combination would not teach or suggest each and every element of the claimed invention.

Applicant respectfully submits that these references would not have been combined as alleged by the Examiner. Indeed, contrary to the Examiner's allegations, the method that is

described by the Teiresias paper has **no relevance** in the context of annotating/characterizing ORFs that Nishikawa. In fact, these references are unrelated, and no person of ordinary skill in the art would have considered combining these disparate references, absent impermissible hindsight.

In fact, these references clearly do not teach or suggest their combination. Therefore, Applicant respectfully submits that one of ordinary skill in the art would not have been so motivated to combine the references as alleged by the Examiner. Therefore, the Examiner has failed to make a prima facie case of obviousness.

Indeed, Applicant would point out that the Examiner expressly concedes that the Teiresias paper teaches the shortcomings of Nishikawa et al. (Office Action at page 8).

Morover, neither Nishikawa, nor the Teiresias paper, nor any alleged combination thereof teaches or suggests However, contrary to the Examiner's allegations, Nishikawa does not teach or suggest *"a processor which: translates an open reading frame (ORF) of said DNA sequence into an amino acid translation; and locates in said amino acid translation occurrences of said patterns from said pattern database to determine whether said open reading frame includes a putative gene in said DNA sequence*", as recited, for example, in claim 1, and similarly recited in claims 16, 23 and 29.

Clearly, these features are not taught or suggested by the Teiresias paper. Indeed, it is important to understand that the claimed invention does not merely include the steps taken in the algorithm described by the Teiresias paper. On the contrary, the claimed invention may USE the Teiresias algorithm in the complete pipeline claimed in the present application.

Further, the Teiresia paper states *vis-a-vis* alignment algorithms that "use of alignment algorithms as a method of identifying conserved patterns among sequences suffers from inherent drawbacks". Nishikawa uses an alignment algorithm in the manner that alignment algorithm were intended originally: find the similarities between two or more sequences while incurring the minimum possible cost.

In short, as previously pointed out to the Examiner, the Teiresias paper discloses an

algorithm (e.g., the Teiresias algorithm) for **discovering** in a biological sequence. In contrast, the claimed invention may **use such patterns which have already been discovered** using the Teiresias algorithm (as disclosed by the Teiresias paper) to identify genes in a DNA sequence.

That is, the Teiresias paper was directed to "pattern discovery", whereas the claimed invention may be considered to be directed to gene identification (e.g., "gene discovery") which involves locating patterns (which have already been discovered) in a DNA sequence. This is completely different than the pattern discovery method disclosed in the Teiresias paper. Indeed, nowhere is gene identification (e.g., "gene discovery") taught or suggested in the Teiresias paper.

Therefore, Applicant submits that these alleged references would not have been combined and even if combined, the combination would not teach or suggest each and every element of the claimed invention. Therefore, the Examiner is respectfully requested to withdraw this rejection.

IV. FORMAL MATTERS AND CONCLUSION

In view of the foregoing, Applicant submits that claims 1-30, all the claims presently pending in the application, are patentably distinct over the prior art of record and are in condition for allowance. The Examiner is respectfully requested to pass the above application to issue at the earliest possible time.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

The Commissioner is hereby authorized to charge any deficiency in fees or to credit any overpayment in fees to Assignee's Deposit Account No. 50-0510.

Respectfully Submitted,

Date: 10/25/05

Phillip E. Miller, Esq.
Registration No. 46,060

McGinn IP Law Group, PLLC
8321 Old Courthouse Road, Suite 200
Vienna, VA 22182-3817
(703) 761-4100
Customer No. 21254

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment was filed by facsimile with the United States Patent and Trademark Office, Examiner C. Dune Ly, Group Art Unit # 2168 at fax number 571-272-8300 this 25th day of October, 2005.

Phillip E. Miller
Reg. No. 46,060